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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/977,866	10/15/2001	Kenneth H. Falchuk	10498-00027	3736

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EXAMINER	
HANLEY, SUSAN MARIE	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 01/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/977,866	FALCHUK, KENNETH H.	
	Examiner	Art Unit	
	Susan Hanley	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Election/Restrictions

Applicant's election of species, with traverse, of regulation of neural tissues in Paper No. 7 is acknowledged. The traversal is on the ground(s) that the subject matter of claim 1-24 is interrelated such that a search and examination of the claims would not be overburdensome. This is not found persuasive because each invention, that is each specific medical condition, is independent and distinct from one another because they require independent searches, particularly with regard to literature searches. Furthermore, the examiner's search is not limited to the class/subclass to which the various species belong. Clearly, a reference which would anticipate one of the species would not necessarily anticipate or even make obvious any of the others. If Applicant does not agree with this statement, a statement by Applicant on the record that the inventions are obvious over one another and that the applicant will accept a reference which renders one specie anticipated or obvious will be accepted as rendering the other groups also anticipated or obvious might be persuasive to rejoining the claims.

An undue burden would ensue from the examination of treatment of multiple disease states. Burden lies not only in the search of US Patents, but in the search for literature and foreign patents and the examination of the language and specification for compliance with the statutes concerning new matter, distinctness and scope of enablement.

The requirement is still deemed proper and is therefore made FINAL.

Specification

The disclosure is objected to because of the following informalities: The specification, as filed, does not provide a brief description of each drawing. The specification provides a brief description for Fig. 7A and incorporates by reference the disclosure of the brief description of the drawings in the provisional application 60/128,653, filed April 8, 1999. The MPEP 608.01 (f) states that:

> When there are drawings, there shall be a brief description of the several views of the drawings and the detailed description of the invention shall refer to the different views by specifying the numbers of the figures, and to the different parts by use of reference letters or numerals (preferably the latter).

The specification references the aforementioned provisional application for the brief description of the remaining figures. A provisional application is never published. Therefore, the public has no access to it in order to determine what disclosure is being incorporated by reference. If the instant application issues as a patent, it will lack a brief description of the drawings and incorporation by reference of the provisional application will not overcome this lack of disclosure.

Appropriate correction is required.

Priority

Applicants claim for domestic priority is acknowledged.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis

added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-24 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-17, 19-20 and 23-25 of copending Application No. 10/008,456. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-18 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 27-43 of copending Application No. 10/008,456 in view of Phelan et al. The claims of the instant application are drawn to a method of modulating cell proliferation or dell differentiation

or a method of promoting cell differentiation by in vitro or in vivo application, as well as a pharmaceutical composition comprising a bilin. Claims 27-43 of application 10/008,456 are drawn to the same methods and composition and further specify that the claimed compound of said method and composition binds to an aryl hydrocarbon (AH) receptor .

Although the mechanism of the binding of bilins by aryl hydrocarbon (AH) receptors is not expressly claimed in the instant application, such binding is deemed inherent in the course of regulation of proliferation or differentiation by bilins. Phelan *et al.* support the inherency of this binding property. Phelan *et al.* teach that bilirubin and biliverdin can directly compete with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCCD) for binding sites on the AH receptor (see p. 159, right column). It is inherent that a bilin would bind such a receptor of any cell encompassed by the scope of the instant claims during the claimed processes. It is noted that the use of an extra reference to show an inherent characteristic of the thing taught by the primary reference is supported in the MPEP 2131. "To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." Continental Can Co. USA v. Monsanto Co., 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991).

This is a provisional obviousness-type double patenting rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9, 21 and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibition of cell proliferation, does not reasonably provide enablement for promoting cell proliferation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. Claims 1 and 21 are drawn to a method of modulating cell proliferation or cell differentiation. Claims 2-9 and 22 are drawn to a method of modulating or regulating cell proliferation. According to Webster's Dictionary, modulating is adapting or adjusting to a certain proportion (p. 762) and regulating is defined as adjusting to a requirement or specification (p. 990). Both words do not limit the direction of the adjustment. That is, they imply that the change in a system can increase or decrease a parameter. Given these definitions, the scope of the instant claims comprise the addition of the claimed substance to cells to promote or inhibit proliferation of said cells. Applicant shows only that the addition of the claimed bilins to a cell culture causes arrest of cell proliferation. The prior art also discloses that the addition of bilins such as biliverdin or bilirubin, effects a decrease in cell proliferation. For example, Janes *et al.* discloses that the addition of unconjugated bilirubin impairs the proliferation of human osteoblasts (Fig. 3,

p. 2583). Likewise, Vsssilopoulou-Sellin *et al.* report that bilirubin inhibited the proliferation of avian chondrocytes in a dose-dependent fashion (Fig. 1, p. 770).

The broadest reasonable interpretation of the terms regulating or modulating is the increasing or decreasing of an activity. The prior art does not suggest that bilins such as bilirubin cause the promotion of proliferative activity. Applicant discloses only inhibition of cell proliferation. Hence, the degree of unpredictability for promotion of proliferation is very high and one of skill in the art would not reasonably expect to achieve an increase in cell proliferation upon the addition of bilins to compositions comprising cells. Absent a further showing, the claims are enabled only for the inhibition of cell proliferation.

Claims 3-4, 11 and 12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting cell proliferation and promoting cell differentiation, wherein concentration of the claimed bilin is in the range of 0.1 to 0.4 μM, does not reasonably provide enablement for inhibition or promotion of cell proliferation and differentiation, respectively, at concentrations greater than 0.1 μM or less than 0.4 μM. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims are drawn to the regulation, by the application of bilins, of cell proliferation or cell differentiation at concentrations of 1 mM or less and 1 μM or less. However, the specification discloses only the inhibition of cell proliferation and the

promotion of cell differentiation by bilins in the range of 0.1 to 0.4 μM, page 83. The specification further discloses that biliverdine causes apoptosis at concentrations equal to or greater than 1 μM and has no effect on cell proliferation or survival at concentration less than 0.1 μM (page 83). The prior art does not disclose that bilins inhibit cell proliferation at levels less than 1 μM (see Janes *et al.*, Figure 3, p. 2583).

Hence, Applicant demonstrates the claimed activities for bilins only in the concentration range of 0.1 to 0.4 μM and specifically discloses that bilins do not inhibit cell proliferation at concentrations less than 0.1 μM and cause apoptosis when the concentration is 1 μM or more. The prior art also does not suggest such a phenomenon. Hence, the degree of unpredictability is very high and one of skill in the art would not reasonably expect to inhibit cell proliferation or promote cell differentiation wherein the concentration of the claimed bilin is in the range of 0.1 to 0.4 μM. Absent a further showing, the claims are enabled for the inhibition of cell proliferation and the promotion of cell differentiation by bilins in the range of 0.1 to 0.4 μM.

Claims 5 and 30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 5 and 13 are drawn to the modulation or regulation of cell proliferation or cell differentiation at concentration of claimed inhibitor of 1 nM or less. The specification discloses only the inhibition of cell proliferation and the promotion of cell

differentiation by bilins in the range of 0.1 to 0.4 μM, page 83. The specification further discloses that biliverdine has no effect on cell proliferation or survival at concentration less than 0.1 μM (page 83). The prior art does not disclose that bilins inhibit cell proliferation at levels less than 1 μM (see Janes *et al.*, Figure 3, p. 2583).

Hence, Applicant demonstrates the claimed activities for bilins only in the concentration range of 0.1 to 0.4 μM and specifically discloses that bilins do not inhibit cell proliferation at concentrations of 0.1 μM or less. The prior art also does not suggest such a phenomenon. Hence, the degree of unpredictability is very high and one of skill in the art would not reasonably expect to inhibit cell proliferation or promote cell differentiation wherein the concentration of the claimed bilin is less than 0.1 μM. Absent a further showing, the claims are not enabled for the inhibition of cell proliferation or the promotion of cell differentiation at a concentration less than 0.1 μM.

Claims 1, 10-17, 21 and 23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for promoting cell differentiation in colon adenocarcinoma cells, does not reasonably provide enablement for promotion of differentiation in any other type of cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims are drawn to a method of modulating cell proliferation or differentiation or promoting cell differentiation with any type of cell with the claimed bilin. Applicant discloses the promotion of cellular differentiation of colon adenocarcinoma cell

lines by the addition of biliverdin to the cell culture. There is no disclosure in the specification of a similar effect on any other type of cells. A survey of the prior art did not yield any report of promotion of differentiation of any type of cell by treatment with a bilin such as bilirubin or biliverdin. The prior art discloses variable effects on cell differentiation by bilins. Sima *et al.*, disclose that continuous infusion of bilirubin suppresses immune response in mice by inhibiting the differentiation of immunocompetent cells (p. 1979, Discussion). Notter *et al.* disclose that bilirubin inhibits the differentiation of mitotically active cells to a greater degree than mature neurons (p. 676, first and second paragraphs). In contrast, Nakajima *et a*l. report that neither bilirubin nor biliverdin has any effect on the differentiation of human leukemia K562 cell line (chart on p. 723). In summary, the prior art discloses only the inhibition or a neutral effect of the claimed bilins on cellular differentiation in cancerous and non-cancerous cell lines.

There appears to be no reliable method that predicts what types of cells will experience promotion of differentiation after contact with a claimed compound. The prior art discloses that bilins can have a neutral or inhibitory effect on cell differentiation. The specification discloses only the promotion of differentiation in colon adenocarcinoma cell lines. The specification does not teach how one of ordinary skill in the art could decide *a priori* when the claimed compounds will promote cell differentiation. The limited disclosure cannot be extrapolated by the skilled artisan to predict which types of cells will experience induction of cellular differentiation by a claimed. Given the great cellular diversity among even related species, it would require

one of ordinary skill in the art undue experimentation to determine what types of cells would undergo an increase in differentiation when contacted with the claimed compounds according to the directions of the instant disclosure. Thus, claims 1, 10-17, 21 and 23 are not commensurate in scope with the enabling disclosure.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9 and 17 are rejected because the metes and bounds of the phrases "other organs arising from the primitive gut" and "etc." are unclear.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 10, 14, 18, 19, 21, 23 and 24 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Rhine *et al.*

The claims are drawn to a method of modulating or regulating cell differentiation comprising treating a cell with a bilin or a claimed compound based on formula I, wherein the cell is contacted *in vitro* and a pharmaceutical composition comprising a bilin or a claimed compound based on formula I.

The broadest reasonable interpretation of modulating and regulating is that there is a promoting or inhibiting effect (vide supra).

Rhine *et al.* teach the inhibition of differentiation of primary cultures of newborn rat cerebral cortical astrocytes by the administration of a solution of bilirubin (see Methods, p. 207) at a concentration of 100 μM or more (p.209, Figures 2 and 3).

Claims 1-3, 6, 10, 14, 18-24 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Notter *et al.*

The claims are drawn to a method of regulating cell proliferation or differentiation comprising treating a cell with a bilin or a claimed compound based on formula I, wherein the cell is contacted *in vitro* and a pharmaceutical composition comprising a bilin or a claimed compound based on formula I.

The broadest reasonable interpretation of modulating and regulating is that there is a promoting or inhibiting effect (vide supra).

Notter *et al.* disclose that bilirubin inhibits the proliferation (p. 677, Table 1 and first paragraph) and differentiation of mitotically active cells to a greater degree than mature mouse neurons (p. 676, first and second paragraphs). The preparation of bilirubin is described in the paragraph on page 673.

Claims 18, 19 and 24 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Sima et al.

Sima et al. disclose a pharmaceutical composition of bilirubin in diluted physiological saline for intravenous infusion into mice (p. 484, Material and Methods, second paragraph).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 7-9 and 15-17are rejected under 35 U.S.C. 103(a) as being unpatentable over Rhine *et al.* or Notter *et al.*

Claims 7-9 and 15-17 are drawn to the regulation of cell proliferation (7-9) and cell differentiation (15-17) in vivo, as part of a therapeutic or cosmetic application wherein the application is to the regulation of neural tissues (specie election).

As discussed in the previous rejection vide supra, Rhine *et al.* and Notter *et al.* teach the inhibition of cell proliferation (Notter et al.) and cell differentiation (both references) *in vitro* in neural cells.

Neither Rhine *et al.* nor Notter *et al.* disclose the inhibition of cell proliferation or cell differentiation *in vivo.*

It would have been obvious to one of ordinary skill in the art at the time the invention was made to inhibit cell proliferation or differentiation in neural tissue *in vivo*

by treatment with a bilin. On page p. 62 of the specification, Applicant states that, "The translation of *in vitro* observations to *in vivo* conditions is greatly facilitated by a number of animal models that are currently in use to evaluate the efficacy of agents for the treatment of cancer." This statement is interpreted to mean that the employment of agents that are successful *in vitro* to *in vivo* usage is conventional because the use of established animal models in the art provides for a reasonable expectation of success for efficacy.

Allowable Subject Matter

The promotion of differentiation in colon adenocarcinoma cells by a claimed bilin appears to be neither anticipated nor obvious over the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Hanley whose telephone number is 703-305-1982. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached at 703-308-4743. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

JEAN C. WITZ
PRIMARY EXAMINER